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Future-proofing regulation for rapidly changing biotechnologies

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Abstract

Our understanding of DNA structure and how it interacts with the environment to give form and function at the organism level is growing at an unprecedented pace which shows no sign of slowing. These developments have already led to many new products and will continue to underpin as yet unpredicted future developments in biotechnology. However, this potential will not be realised unless the mechanisms for risk assessment, regulatory approval, product claims and labelling etc. are fit for purpose, have the confidence of all stakeholders and are sufficiently agile to support this rapidly changing field. The sectors that are making particular advances in biotechnological processes include agriculture, pharmaceuticals, food, chemical and human diagnostics and therapeutics. In many of these areas the research, investment and innovation pipeline is operating well as evidenced by the many marketed products. However, developments in plant breeding methods have posed particular challenges for regulators which in turn is stifling R&D and innovation, particularly in the EU. In rapidly moving areas of research and development, it is imperative that regulatory frameworks are future-proofed by design.

Article

Biotechnology is a key component of the global knowledge-based economy which is expected to be worth 727.1 billion USD by 2025 (Grand View Research 2017). Sectors that are making particular advances using biotechnology include agriculture, pharmaceuticals, food, chemical and human diagnostics and therapeutics. The growth in these applied biotechnologies has been driven by rapid developments in more fundamental areas of science such as DNA sequencing, computational bioinformatics, molecular genetics, cell biology, fermentation technologies etc.

Progress in DNA sequencing neatly illustrates how underpinning science can be rapidly translated into new processes and biotechnology products. Thirty years ago, sequencing DNA was laboriously slow and expensive, and confined to specialist research laboratories. However, over the last twenty years, a series of breakthroughs in sequencing technologies (so called Next Generation Sequencing platforms) have resulted in exponential growth of nucleotide data. The European Nucleotide Archive (ENA 2018) currently holds sequences comprising almost 9000 trillion (8.9×1015) DNA bases and is increasing at a rate of over 90 million bases per second and with a doubling time of just 2 years! This has come with a commensurate reduction in price; the first human genome in 2002 cost an estimated 3 billion USD (NGSRI 2013) with the library preparation and sequencing per se, accounting for about half. However, the same amount of sequence data today cost around 1000 USD and is enabling a wide spectrum of both research and commercial applications. One example is non-invasive pre-natal testing for genetic abnormalities. For example, tests for trisomy 21 (and other chromosomal aneuploidies) were first introduced in 2011 and are being described as the fastest growing genetic tests in medical history (Paxton 2017). It was estimated that 4–6 million pregnant women per year were utilising the test worldwide by 2017 but this will likely be over 15 million by 2027 (Green et al. 2017).

Our expanding knowledge of DNA sequence combined with microbial pathway engineering, automation of fermentation technologies and purification methodologies has also led to an expansion in industrial biotechnology with many thousands of commercially available enzymes, bulk- and high-value chemicals including biopharmaceuticals, food colourings, flavourings etc. produced by genetically engineered microbes. These technologies drove the switch in the mid-1980s from bovine or porcine insulin extracted from animal pancreases for treatment of diabetes to production from recombinant microbes carrying the human insulin gene. Over the last few years, classical human insulin is being replaced, at least in developed countries, by a switch to designer 'synthetic biology' variants encoding insulin analogues not found in nature with extended duration of action or different absorption rates.

The examples described above have significant ethical and safety implications, however, the rapid and worldwide adoption of these and many other products of medical and industrial biotechnology shows that innovation and commercialisation of potentially controversial biotechnologies is possible where societal needs are met and regulatory oversight is functioning well.

Commercialisation of agricultural biotechnology has been far more regionalised and generally has fared less well. Some countries have accommodated almost 100% adoption of a narrow range of genetically modified crops while other countries have a zero tolerance of the same crops or food/feed derived from them and have failed to authorise identical events even after thorough risk assessment concludes that it is safe to do so. Particularly in EU, the authorisation and risk management process is highly politicised where the outcomes of a rigorous, science-based risk assessment are marginalised and where different member states take opposite positions on adoption for cultivation while facilitating the import of the same crop variety for food and feed uses. There are compelling reasons why, with good management, the products of future biotechnologies can be part of the solution for the many different challenges facing global agricultural and food supply. However, this potential will be realised only when the mechanisms for risk assessment, regulatory/ethical approval, product claims and labelling etc. are fit for purpose and have the confidence of all stakeholders. Particularly in rapidly advancing fields, these regulatory mechanisms must be future-proofed by design to be sufficiently agile to address future developments and challenges. This may help to engender confidence in the regulatory process and in turn, help to inform and diffuse the highly polarised societal arguments over modern plant breeding methods.

Thirty-five years after the first genetically modified organisms (GMO) were commercially cultivated, one would expect that at least the trigger for risk assessment and regulation would have been broadly agreed. However we see major differences with products regulated as GMOs in one country and not another (and vice versa). We also see inconsistencies and uncertainties where, for example in EU, identical new plant types could in theory be classified under law as a GMO or a non-GMO depending on precise breeding methods used to make them. Also in the EU it is not even certain in law whether a plant possessing no recombinant DNA as a consequence of genetic segregation is a GMO or not! There are also a raft of new, game-changing biotechnologies coming along the innovation pipeline that do not neatly fit the existing definitions or frameworks, such as gene editing, gene drives, reverse breeding, topically-applied gene silencing etc. Thirty-five years of experience of GMO cultivation and marketing along with a raft of new technologies on the horizon must surely be sufficient to trigger a radical overhaul of GMO regulations to future-proof them and avoid some similar issues going forward. Many countries outside the EU have recently done, or are currently in the process of doing, just that. For example, in 2016 the Office of the Gene Technology Regulator in Australia sought stakeholder views as part of a Technical Review of their Gene

Technology Regulations. Amendments to the 2001 regulations were proposed and are currently passing through the legislative forum. The amendments included clarification that neither null segregants nor organisms with simple gene edits are GMOs.

Argentina, in 2015, was one of the first countries to update their existing GMO regulatory framework to accommodate products derived from innovative breeding techniques. This new regulation (#703/2015) wisely avoided using terms such as 'genome editing' or 'reverse breeding' which themselves encompass a range of meanings but instead set up a product-by-product, 60-day consultation procedure including a diagrammatic decision tree to establish the regulated status of any new crop variety (Whelan and Lema 2015). The new regulation states that plants resulting from site-directed mutagenesis that contain no transgene or new combination of genetic material are not included in the framework for GMOs.

Brazil and Chile have taken similar steps with Normative Resolutions signed in 2018 and 2017 respectively. Both introduce a consultation step to decide, on a case-by-case basis, whether a product of innovative breeding falls under the existing GMO regulations. Initial interpretations of both new laws indicate that simple site-directed mutagenesis would be exempt from GMO regulation. Japan is actively looking at their regulatory oversight of varieties developed using innovative breeding. In a meeting of the Japanese Ministry of the Environment expert committee on 20th Aug 2018 it was decided that gene editing resulting in elimination of gene function that could occur naturally would not fall under the biotechnology legislation. However, the final committee recommendations are not expected until March 2019.

In 2015, the USA embarked on a major modernisation of its regulatory system for biotechnology products. The US federal government recognised that 'advances in science and technology have altered the product landscape rapidly and that the complexity of the current regulatory system can make it difficult for the public to understand how the safety of biotechnology products is evaluated and creates challenges for small and mid-sized businesses navigating the regulatory process for these products'. Thus, a call for public comments and series of public meetings were held and an update to the Coordinated Framework for the Regulation of Biotechnology was initiated to 'help product developers and the public understand what the regulatory pathway for products might look like'. Together with the National Strategy for Modernising the Regulatory System for Biotechnology Products (EOP 2016), the 2017 update on the Co-ordinated Framework (EOP 2017) offers a complete picture of a robust and flexible regulatory oversite for products of modern biotechnology.

This contrasts starkly with the apparent lack of progress of EC regulators which is surprising considering the highly active research community within the member states and the fact that the EU is the second largest importer of GM products in the world (FAS.USDA 2018). DG SANCO initiated a New Technologies Working Group in 2008, to evaluate whether plants derived using various categories of NPBTs fell under EU GMO legislation or not. The report was finalised in 2012 and concluded that some iterations of NPBTs should be regulated as GMOs while others should not. However, the report was never made public. Also in 2012 the EC mandated EFSA to deliver a scientific opinion related to risk assessment of plants developed using the zinc finger nuclease 3 technique (ZFN-3) which allows the integration of gene(s) in a predefined insertion site in the genome of the recipient species. EFSA concluded in line with general scientific consensus that the risks associated with the range of possible outcomes using ZFN-3 were comparable to conventional transgenesis except that it could minimise hazards associated with disruption of genes and/or regulatory elements in the host genome (EFSA 2012). The EC have also received inputs from many scientific bodies and NGOs including the European Academies' Science Advisory Council's report

'Genome editing: scientific opportunities, public interests and policy options in the European Union' (EASAC 2017). The EC requested their high level Scientific Advice Mechanism write an explanatory note on 'New Techniques in Agricultural Biotechnology' (SAM 2017); and most recently, the European Court of Justice delivered a ruling on four specific questions posed by the French State Council which included the interpretation that targeted mutation breeding is not exempted from the EC 2001/18 regulation in the same way that classical untargeted mutagenesis is. Thus, significant uncertainty and disproportionality remains in the interpretation of EU GMO regulation and even after a protracted time period, EC risk managers seem unwilling to act. For example, it is wholly disproportionate and illogical for the EC to use GMO legislation to regulate targeted mutations that could be found naturally in wild or cultivated populations of the same crop, and at the same time to exclude potentially more disruptive mutations generated randomly with ionic radiation from the regulation. I urge a rethink on this issue. However, from the lack of EC reaction to the ECJ ruling to date, that indeed seems to be their intention. If so, the commission must urgently work with applicants, member state competent authorities, the JRC and EFSA to facilitate a streamlined route through the GMO application process for products of simple gene editing. This should include differentiated and proportionate risk assessment procedures and unique identifier protocols (or exemptions for the cases this is not possible). There is clear scope for this under EC 2001/18 Article 7.

In the broader sense, the challenge over regulating simple gene editing is merely the tip of a huge iceberg that touches our personal bias and lack of dialogue around biotechnology, agricultural sustainability, innovation, choice in the food supply chain etc. EU politicians and commissioners need to show leadership to breakdown the polarised positions on biotechnology and to initiate an overhaul of EU GMO regulatory procedures to make it fit-for-purpose now and future-proofed for the next thirty years of research and innovation.

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